

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

AVERMECTIN B1

SB 950-non-assigned, Tolerance # 50406

March 16, 1987

Revised November 22, 1988; June 16, 1989; March 14, 1990

I. DATA GAP STATUS

Combined Rat: (Chronic + Onco)	No data gap, no adverse effect
Chronic Dog:	No data gap, no adverse effect
Combined Mouse: (Chronic + Onco)	No data gap, possible adverse effect (not onco)
Repro Rat:	No data gap, possible adverse effect
Terato Rabbit:	No data gap, no adverse effect
Terato Mouse:	No data gap, possible adverse effect
Gene Mutation:	No data gap, no adverse effect

Chromosome: No data gap, no adverse effect
DNA Damage: No data gap, no adverse effect
Neurotox: Not required at this time

-----**Note, Toxicology**
one-liners are attached

** indicates acceptable study
indicates study on file, not yet reviewed
Bold face indicates possible adverse effect

File name: T900314
Revised by G. Chernoff, 3/14/90

Record numbers through 086100, and Volumes through 147, listed by the Pesticides Registration Library as of 3/14/90, have been rectified with those listed in the Toxicology Summary.

II. TOXICOLOGY SUMMARY

COMBINED (CHRONIC/ONCOGENICITY) TOXICITY, RAT

**013, 016-025; 046635, 046641-046650, "MK-0936: 105 Week Carcinogenicity and Toxicity Study in Rats with 53 Week Interim Necropsy", (Merck, Sharp and Dohme Research Labs., Report TT#82099 0 - interim report, pilot study, final report - Vol. 8, 5/29/85). Abamectin (Avid), 89-91%; 0 (acetone), 0 (acetone), 0.75, 1.5, 2.0 (increased to 2.5 at week 11 and decreased to 2.0 at week 13) mg/kg, 65/sex/group, two control groups; few animals with tremors at >2.0 mg/kg. NOEL = 1.5 mg/kg based on tremors at the next highest dose level. Originally evaluated as unacceptable but upgradeable. (Hathaway, 8/7/86). Additional data (056 052064) supplied and study considered ACCEPTABLE. (Hathaway, 1/7/87).

056 052064, Dietary analysis, statistical analysis of food consumption, organ weight and clinical parameters and GLP statement provided. (Hathaway, 1/7/82).

CHRONIC TOXICITY, DOG

**012 046634, "Fifty-three Week Dietary Toxicity Study in Dogs", (Merck Sharp & Dohme Research Laboratories, TT #82-104-0, 5/23/84). Abamectin (at least 89% avermectin Bla and avermectin B1b; MK-0936 identified as L-676,863-00V54); 0 (acetone), 0.25, 0.50, 1.0 mg/kg/day by feeding to 6 males and 6 females per group for 52 weeks. No adverse effects. NOEL = 0.25 mg/kg/day (mydriasis). ACCEPTABLE. Davis 8/7/86, 11/14/88.

015 046637, Twelve-Week Oral Range-Finding Study in Dogs - Pilot study for 012 046634.
No review.

010 046627, "Eighteen Week Oral Toxicity Study in Dogs," (Merck Sharp & Dohme Research Laboratories, Report TT 76 073 0, no date). A Subchronic Oral Toxicity Study. Avermectin Bla, purity not indicated; 0 (sesame oil), 0.25, 0.5, 2.0, 8.0 mg/kg/day by gavage to 3 males and 3 females per group for 17 to 17.5 weeks. **Adverse effects:** whole body muscular tremors, ataxia, mydriasis, ptyalism, tonic convulsions, emesis, body weight decreases, and among animals which died or sacrificed prior to schedule termination, hepatocellular vacuolation and gallbladder edema. NOEL = 0.25 mg/kg/day. Supplemental. (BKDavis, 8/6/86).

ONCOGENICITY, RAT

See Combined Chronic/Onco above

COMBINED (CHRONIC/ONCOGENICITY), MOUSE

****026-031; 046651-046656**, "MK-0936: Ninety-Four Week Carcinogenicity and Toxicity Study in Mice", (Merck, Sharp & Dohme Research Laboratories, antemortem report, tables, methods, etc., 6-20-86). Abamectin, 89.0 - 91.1%, 0 (acetone), 0 (acetone), 2, 4, & 8 mg/kg/day, 50/sex/group, 2 control groups plus 12/sex/group for 6 and 12 month sacrifices. **Possible adverse effect - Increased mortality** at 4 and 8 mg/kg/day. NOEL = 2 mg/kg/day. Originally reviewed as unacceptable but upgradeable. (Carlisle, 8/13/86). Additional data (056, #052069), supplied and study considered ACCEPTABLE. (Carlisle, 1/6/87).

056 052069, Missing pages (2301 - 2305), indicates Good Laboratory Practices compliance. (JCC, 1-6-87).

REPRODUCTION, RAT

****014 046636**, "Reproductive Effects of MK 0936 Administered Orally by Gavage to Cr1:COBS CD (SD)BR Rats for Two Generations", (Argus Research Laboratories, report TT #82-901-0, 1984). Avermectin, no purity stated; 30/sex/group were given 0 (sesame oil), 0.05, 0.12 or 0.40 mg/kg/day by oral gavage for 2 generations, 2 litters per generation. Parental NOEL > 0.4 mg/kg, Repro NOEL = 0.12 mg/kg (pup survival and weight). Originally reviewed as unacceptable, JGee, 8/12/86 and JAParker, 8/25/86. Additional data supplied, (056 #052066 and 058 # 052590, 052591) and study now ACCEPTABLE. **Possible adverse effect.** (JGee, 1/8/87, 2/26/87; JAParker, 2/26/87).

011 046633, Summary of 014 046636.

056 052066; 058 052590, supplementary information: Necropsy on F0 adults, clinical observations for F0, F1 males and females, eyes - clarified, and test substance purity and stability information. (JGee, 1/8/87 and JAParker, 2/26/87).

NOTE: The next three (3) studies are preliminary studies to study 014 046636 and should be considered supplemental, not unacceptable as previously noted. (JAParker, 8/10/88)

015 046639, "MK-0936: Oral Range-Finding Study (Multigeneration) in Rats", (Merck, Sharp and Dohme Research Laboratories, TT #82-707-0, 1-6-84). Avermectin, 94%, 12 females/group were given 0 (aqueous 1% v/v propylene glycol plus 0.6% v/v dicotyl sodium sulfosuccinate), 0.15, 0.5, 1.5, or 5.0 mg/ml in drinking water for 15 days before mating through day 21 of lactation. Nominal maternal NOEL = 1.5 mg/ml; nominal neonatal NOEL = 1.5 mg/ml (neonatal weight gain and mortality). (Gee, 8/11/86).

009 046626, "C-076 (Bla): Oral Reproduction Study in Rats", (Merck, Sharp and Dohme Research Laboratories, no date, TT #77-712-0). Avermectin Bla, lot 00P22, no purity stated, 12 females/group (2 control groups) were given 0 (sesame oil), 0.1, 0.2, or 0.4 mg/kg/day by gavage 14 days before mating through day 21 post partum; maternal NOEL = 0.4 mg/kg (HDT); Repro NOEL = 0.1 mg/kg (spastic movements of pups); no histology, (JGee, JAParker, 8/8/86).

009 046625, "C-076(Bla): Oral Reproduction Study in Rats", (Merck, Sharp and Dohme Research Laboratories, no date, TT# 77-706-0). Avermectin Bla, lot P-20 (no purity stated); 12 females/group (2 control groups) were given 0 (sesame oil), 0.5, 1.0, or 2.0 mg/kg by gavage for 15 days before start of mating; 2.0 mg/kg reduced to 1.5 mg/kg after 5 doses; maternal NOEL = 1.0 mg/kg; Repro NOEL < 0.5 mg/kg (pup weight and survival). (Gee, Parker, 8/8/86).

REPRODUCTION, RAT
DELTA 8,9-ISOMER OF AVERMECTIN B1

120 071744, "Delta 8,9-Isomer of Avermectin B₁ Single Generation Study in Rats", (Merck Sharp and Dohme, TT #87-716-0, 6/7/88). L-652,280-000N, 91.6% pure, Lot # L-652,280-000N005, was administered by oral gavage to groups of 20 Cr1:CD (SD) BR female rats at doses of 0, (sesame oil vehicle control), 0.06, 0.12, and 0.40 mg/kg/day from fifteen days prior to cohabitation through day 20 of lactation. There were no signs indicating a MTD was achieved during the course of this study, and no treatment related maternal or reproductive findings, including gross and histomorphological eye examinations on weanling-aged offspring, were reported. The maternal and reproductive NOEL = 0.40 mg/kg/day (HDT). Supplementary study with no adverse health effects noted (G. Chernoff, 3/7/90).

REPRODUCTION, RAT
IVERMECTIN

146 085374, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #78-713-0/-1, 11/11/80). MK-933 (lot #'s 00W03, 00W08, 00W12, 00W19, and 00W40, >98% purity) was administered by oral intubation to groups of 20 female and 10 male CRCD rats at doses of 0 (sesame oil vehicle control), 0.4, 1.2, and 3.6 mg/kg/day. The study, which was designed for continuous treatment throughout production of two litters in each of three generations, was terminated early (at weaning of the F-1a litters for the high dose group, and following production of the F-2a litters for the 0.4 and 1.2 mg/kg groups) because of high neonatal mortality. A NOEL could not be determined. Supplemental study with possible adverse health effects (neonatal mortality) noted (G. Chernoff, 3/8/90).

146 086098, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #78-724-0, 11/11/80). MK-933 (lot #'s 00W12, 00W19, and 00W40, >98% purity) was administered by oral intubation to groups of 20 female and 10 male CRCD rats at doses of 0 (sesame oil vehicle control), and 2.0 mg/kg/day for 20 weeks, beginning 11 weeks prior to mating and continuing

through weaning of 1 litter (F-1a). The study, which was designed for continuous treatment throughout production of two litters in each of three generations, was terminated early because of high neonatal mortality in a concurrent MK-933 reproduction study (CDFA Record No. 085374) utilizing similar dose levels. In the study under review, increased neonatal mortality was observed in the treatment group, and a NOEL could not be determined. Supplemental study with a possible adverse health effect (increased neonatal mortality) noted (G. Chernoff, 3/8/90).

147 085375, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #79-706-0/-1, 11/11/80). MK-933 (lot # L-640,471-00W51, >97.78% purity) was administered by oral intubation to groups of 20 female and 10 male CRCD rats at doses of 0 (sesame oil vehicle control), 0.05, 0.1, 0.2, and 0.4 mg/kg/day for 70 days prior to mating, and continuing through 2 generations, 2 litters per generation. Pre-mating maternal weight gains were reduced in high dose group females; in the F-2 offspring, neonatal mortality was increased at 0.2 and 0.4 mg/kg and pre-weaning mortality was increased at the high dose. A treatment-related increase in MK-933 residues was found in both the plasma and liver. The systemic NOEL = 0.2 mg/kg/day (reduced pre-mating weight gain); and the reproductive NOEL = 0.1 mg/kg/day (increased neonatal mortality). Supplemental study with a possible adverse health effect (increased neonatal mortality) noted (G. Chernoff, 3/12/90).

145 085373, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #79-706-2, 6/18/81). In this continuation of the multigeneration study reported in CDFA Record No. 085375, MK-933 (lot # L640,471-00W51, >97% pure) was administered by oral intubation to groups of 20 female and 10 male F-2b CRCD rats at doses of 0 (sesame oil vehicle control), 0.05, 0.1, 0.2, and 0.4 mg/kg/day (corresponding to their parents dosages) from weaning through the production and weaning of 2 litters (F-3a & F-3b). Pre-mating parental weight gains were reduced in the mid and high dose groups; mean live litter size and pup survivability were decreased, and kidney cysts increased in the high dose group offspring; and a treatment-related increase in MK-933 residues was observed in the plasma and liver. The systemic NOEL = 0.1 mg/kg/day (reduced pre-mating weight gain); and the reproductive NOEL = 0.2 mg/kg/day

(decreased litter size and increased neonatal mortality). Supplemental study with a possible adverse health effect noted (G. Chernoff, 3/8/90).

147 086099, "MK-933: Cross-Fostering Study in Rats", (Merck Sharp and Dohme, TT #79-710-0, 11/11/80). MK-933 (lot # L-640,471-00W51, >97.78% purity) was administered by oral intubation to groups of 40 female CRCD rats at doses of 0 (sesame oil vehicle control), or 2.4 mg/kg/day for 61 days prior to mating, and continuing through day 20 postpartum. Within 24 hours of birth, all the litters were cross-fostered into 1 of four groups: group 1 from treated dams to treated dams (treated treated); group 2 control treated; group 3 control control; and group 4 treated control. The study was terminated 13 weeks postpartum. Pup mortality was significantly increased between days 8 and 14 postpartum in groups 1 and 2 and pup body weights were decreased. Body weights through week 13 were also decreased in groups 1 and 2, as well as in group 4. The results of this study indicate that the neonatal mortality observed in the other rat reproduction studies may be attributed to postnatal exposure to the test compound through maternal milk. A reproductive NOEL cannot be established from this study. Supplemental study with a possible adverse health effect (increased pup mortality) noted (G. Chernoff, 3/12/90).

147 086100, "MK-933: Metabolism Study in the Rat", (Merck Sharp and Dohme, TT #79-711-0, 11/11/80). Tritium labeled MK-932 (lot # L-638,709-11X0, 97.6% purity, specific activity of 0.2 mCi/mg) was administered by oral intubation to 2 groups of 6 female CRCD rats at doses of 2.5 mg/kg/day. Treatment was administered to a chronic group 61 days prior to mating through day 9 postpartum, and to an acute group from days 1 through 9 postpartum. In the chronic group, MK-932 plasma levels increased until treatment day 10, after which time they remained relatively constant except on postpartum day 1, when they were significantly higher. Throughout the study period, erythrocyte levels were one-half to one-third the plasma levels. In the acute group, plasma levels increased with length of treatment, and reached chronic levels on postpartum day 10. MK-932 tissue levels were highest in the kidneys from chronic group females, and were lowest in brains from both groups of females. Milk levels from both groups were 2 to 3 times higher than the corresponding maternal plasma levels on day 4, 6 and 10 postpartum, and pup consumption approached the LD-50. Pup plasma levels increased

dramatically from days 1-6 postpartum, and were approximately 3 times higher than the maternal plasma level by day 6. Both liver and brain MK-932 levels paralleled the increase in pup plasma levels, with the brain reaching its highest concentration on day 6 postpartum, after which time it dropped to approximately one third the plasma level. Supplemental study (G. Chernoff, 3/12/90).

144 085366, "Developmental Changes in Metabolism and Transport Properties of Capillaries Isolated from Rat Brain", A.L. Betz and G.W. Goldstein, J. Physiol. (1981), 312:365-376. Capillaries were isolated from the cerebral cortices of an unspecified number of SD rats, at 1, 5, 10, 15, 21, 30, and 45 days of age, and investigated for the time in development of metabolic and transport aspects of the blood-brain barrier. The results indicated that various aspects of brain capillary functions showed distinct developmental patterns which may be related to changes in blood-brain barrier permeability during development. Supplemental journal article (G. Chernoff, 3/13/90).

144 085367, "Ontogeny of the Blood-Brain Barrier", N.R. Saunders, Exp. Eye Res. (1977), Suppl:523-550. The morphology of development of the blood-brain and blood-CSF barriers, the development of the blood-brain barrier to non electrolytes, the penetration of protein from plasma into CSF and brain in fetal sheep, and the effects of adverse conditions on barrier permeability during development, are all reviewed in this article. Among the many conclusions reached, is that the critical period for the development of a number of different blood-brain barrier mechanisms occurs between 50 and 70 days gestation in sheep, and during the neonatal period in rats. Supplemental journal article (G. Chernoff, 3/13/90).

144 085371, "Effects of Ivermectin on Reproduction and Neonatal Toxicity in Rats", (G.R. Lankas, D.H. Minsker, and R.T. Robertson; submitted for publication in Food and Chemical Toxicology, no date given). This article, submitted for publication, is based on 6 studies (CDFA Record Nos. 085373-085375, and 086098-086100) listed above. This is supplemental information and no worksheet has been provided (G. Chernoff, 3/14/90).

SUMMARY of Ivermectin Rat Reproduction Studies: Combining the data provided in CDFA Records 085375 and 085373 and considering the collective data from 3 generations (2 litters per generation), the reproductive NOEL = 0.2 mg/kg/day, and an adverse health effect (increased neonatal mortality) is noted. The cross-fostering study in CDFA Record 086099 indicates that the adverse effect is a postnatal event, occurring in the early stages of lactation. The metabolism study in CDFA Record 086100 demonstrates that the level of Ivermectin in maternal milk is approximately 3 times higher than in the maternal plasma, suggesting that the perinatal pups are consuming quantities of Ivermectin in the LD-50 range. Since the blood-brain barrier is not fully developed in the neonatal rat (CDFA Record 085367), it is hypothesized that the Ivermectin in the lactating dams milk passes to the neonatal pup and enters the brain, thereby, resulting in the observed neonatal mortality (G. Chernoff, 3/14/90).

TERATOLOGY, RAT

**032 046659, "I. Oral Range-finding Study in Pregnant Rats and Oral Teratogenic Study in Rats", (Merck, Sharp and Dohme Research Laboratories, reports TT #82-705-1, #82-705-0 11-10-82). Avermectin, 94%, pilot study with 10/group at 0 (sesame oil), 0.25, 0.5, 1.0, and 2.0 mg/kg by gavage days 6 - 17, 1 death at 2.0 mg/kg. Full Study with 25/group at 0 (sesame oil), 0.4, 0.8, 1.6 mg/kg by oral gavage days 6 - 19; nominal maternal NOEL = 1.6 mg/kg, nominal terato/feto NOEL = 1.6 mg/kg/day. Originally reviewed as unacceptable but upgradeable, JGee, 8/8/86 and JAParker, 8/28/86. Additional data received (057 # 052070 and 058 # 052581) made study ACCEPTABLE. No adverse effect. (JAParker, 2/26/87).

057 052070, Supplemental information: Individual fetal data by dam and individual clinical observations for pilot study TT 82-705-1 and for study TT 82-705-0. (Parker, 2-26-87).

058 052581, Analysis of dosing suspension for Teratogenic study in rats (032 046659). (Parker, 2-26-87)

032 046657, "Exploratory Teratology Studies in the Rat," (Merck, Sharp and Dohme Research Laboratories, report TT 77-701-0" 4-21-82). Avermectin Bla (no purity stated), range-finding study, 20 females/group (2 controls) given 0 (sesame oil), 0.8, 1.6 or 3.2 mg/kg/day by oral gavage on days 6 - 15; 3 deaths at the high dose, maternal NOEL = 1.6 mg/kg, Teratogenic NOEL not established since only control and high dose fetuses were examined for visceral and skeletal findings, External teratogenic NOEL = 1.6 mg/kg. Supplemental. (JG 8-8-86, JAP 8-28-86).

010 46628, Fourteen-Week Oral Toxicity Study in Rats Following In Utero Exposure. Supplemental histology. No review/worksheet. (Kishiyama, 11/14/88).

TERATOLOGY, RAT
DELTA 8,9-ISOMER OF AVERMECTIN B1

120 071743, "Delta 8, 9-Isomer, Avermectin B₁ Oral Developmental Toxicity Study in Rats", (Merck Sharp and Dohme, TT #87-715-0, 6/7/88). L-652,280-000N, Lot # L-652,280-000N005, 91.6% pure, was administered by oral gavage to groups of 25 Crl:CD (SD) BR mated female rats at doses of 0 (sesame oil vehicle control), 0.25, 0.5, and 1.0 mg/kg/day on day 6-17 of gestation. There were no signs indicating a MTD was achieved during the study. While maternal weight gain was significantly increased at 0.5 and 1.0 mg/kg during the treatment period, there were no adverse treatment related maternal or developmental effects reported. Maternal and developmental NOEL = 1.0 mg/kg (HDT). Supplemental study with no adverse health effects noted (G. Chernoff, 3/7/90).

TERATOLOGY, RABBIT

**032 046660, "II. Oral Range-finding Study in Pregnant Rabbits and Teratogenic Study in Rabbits", (Merck, Sharp and Dohme Research Laboratories, report TT #82-706-1, #82-706-0, 11-10-82, Range-finding at 0 (sesame oil), 0.5, 1.0, 2.0 or 3.0 mg/kg/day by gavage on days 6-18.

Full study at 0, 0.5, 1.0, or 2.0 mg/kg/day by gavage on days 6-27. Maternal NOEL = 1.0 mg/kg/day, Teratogenic NOEL = 1 mg/kg/day. Originally reviewed as unacceptable but upgradeable, (JG, 8-8-86, JAP, 8-28-86). Additional data were supplied (057 # 052071 and 058 # 052581) and the study is considered ACCEPTABLE. No adverse effect. (Parker, 2/26/87).

057 052071, Supplemental information: Individual fetal data by dam and workbook pages with clinical observations and food consumption data. (Parker, 2/26/86)

058 052581, Dosing solution analytical results. (Parker, 2/26/86).

032 046658, "Oral Range-finding Exploratory Teratology Studies of Avermectin Bla in the Rabbit", (Merck, Sharp and Dohme Research Laboratories, report TT 76-724, 77-702-0/1", 4/21/82). Avermectin Bla (no purity stated, no lot number), Pilot at 0 (sesame oil), 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg/day. Full study (2 studies with a combined total of 25/dose group, 2 control groups) given 0, 0.25, 0.5, or 1.0 mg/kg/day by gavage on days 7 - 16. Apparent maternal NOEL = 1.0 mg/kg, apparent developmental NOEL = 1.0 m/kg. (JGee, 8-8-86, JAParker, 8-28-86).

TERATOLOGY, MICE, CF-1 strain

009 046622, "Oral Teratogenic Evaluation in Mice", (Merck Sharp and Dohme, report TT #76-723-0/1/2/3, no date given). Avermectin Bla and B2 (no purity given), 2 replicate studies, with 10 and 15 /group = 25 total. Given 0 (sesame oil), 0.1, 0.2, 0.4, or 0.8 mg/kg/day by gavage on days 6 - 15, For Bla, Maternal NOEL < 0.1 mg/kg (mortality), Teratogenic NOEL = 0.2 mg/kg. For B2, Maternal NOEL < 0.1 mg/kg, Teratogenic NOEL = 0.1 mg/kg. Tremors at all doses, no repro effects noted. Cleft palate seen in fetuses. Range finding studies conducted to 8.0 mg/kg/day with tremors, coma and death as the signs of maternal toxicity. **Adverse effect.** Initially reviewed as unacceptable; Gee, 8/6/86, JAParker, 8/28/86. Additional data submitted, 057, # 052072 (individual fetal observations and clinical observations). Analysis of dosing solutions was not performed. Study STILL NOT ACCEPTABLE. (JAParker, 1/12/87).

057 052072, Supplemental information: individual fetal observations and clinical observations. (Parker, 1-12-87).

009 046623, "Oral Teratogenic Evaluation in Mice", (Merck, Sharp and Dohme, report TT #77-705-0", no date); Avermectin B_{1a} (no purity stated); 20/group (2x20 for controls) were given 0 (sesame oil), 0.1, 0.2, 0.4 or 0.8 mg/kg days 6-15 by oral gavage; Maternal NOEL < 0.1 mg/kg (tremors); Terat NOEL = 0.2 mg/kg (cleft palate) **adverse effect**. Upgradeable. Initially reviewed as unacceptable; Gee, 8/6/86, Parker, 8/28/86. Additional data submitted, 010, #046629 (fetal observations). Analysis of dosing solutions was not performed. Study still NOT ACCEPTABLE. (Parker, 1/12/87).

009 046624, "Ten-day Oral Toxicity Study in Pregnant Mice", (Merck, Sharp and Dohme report TT #77-717-1", no date). Avermectin B_{1a}, no purity stated; 20 per group given 0 (sesame oil), 0.025, 0.050, 0.075 or 0.10 mg/kg by oral gavage days 6-15; low pregnancy rate; maternal NOEL = 0.05 mg/kg; no data on fetuses - no terat NOEL available due to lack of data. Supplemental. (Gee, 8/6/86, 8/13/87 and Parker 3/13/87).

010 046630, "Ten-day Dietary Maternotoxicity Study in Mice", (Merck, Sharp, and Dohme, report TT 83-705-1, 1984). Avermectin approximately 88% (Tritiated at > 98%), nominal 0 (acetone), 0.1, 0.3, or 0.6 mg/kg/day, days 6-15 in the diet: NOEL = 0.1 mg/kg/day (actually, 0.06 due to diet intake and content). Supplemental. (Gee, 8/7/86).

TERATOLOGY, MOUSE CF-1 Strain
DELTA 8,9 ISOMER OF AVERMECTIN B1

****036 046683**, "8,9 Isomer of Avermectin B1 Maternotoxicity and Teratology Studies", (Merck, Sharp & Dohme, report TT 84-722-0, 1-8-86). (8, 9-Avermectin B_{1a}, 99%, L-652,280-00N); 8-13 Females per group given 0 (sesame oil), 1.5, 3.0, 6.25, 25.0, or 50 mg/kg/day, 6-15 of gestation; no survivors in ≥ 3 mg/kg; NOEL's not established; 24/83 fetuses in 4/7 litters had cleft palate in 1.5 mg/kg (**adverse effect**), 0 in control; originally reviewed as unacceptable.

Gee, 8/8/86, Parker, 8/28/86. Additional data supplied, analysis of dosing solutions, 058 # 052592, and study now ACCEPTABLE. (JAP 3/13/87).

****036 046684**, "Oral Maternotoxicity Study in Mice", (Merck Sharp and Dohme, report TT 84-722-1; 1/8/86). (8,9 Isomer of avermectin B_{1a} 99%); 12 females per group were given 0 (sesame oil), 0.05, 0.10, 0.50 or 1.0 mg/kg by oral gavage days 6 - 15. Terato NOEL = 0.05 mg/kg (Cleft Palate)(**adverse effect**); maternal NOEL = 0.10 mg/kg; ORIGINALLY reviewed as unacceptable (missing data, animal number). Gee, 8/8/86, Parker, 8/28/86. Additional data received, 058 # 052592, analysis of dosing solutions and study now ACCEPTABLE. (JAP 3/13/87).

****046685**, "8,9 Isomer of Avermectin B₁ (L-652,280-00N) III Oral Teratology Study in Mice, TT #85-710-0." (Merck, Sharp and Dohme, 1/8/86). Avermectin, 8,9 isomer of B₁, 99% purity, 25 females per group were given 0 (sesame oil), 0.015, 0.03 or 0.06 (nominal) mg/kg/day, day 6-15; by oral gavage; study to confirm NOEL values; maternal NOEL \geq 0.06 mg/kg, developmental NOEL \geq 0.06 mg/kg; initially reviewed as unacceptable but upgradeable with a possible adverse effect of exencephaly and a NOEL of 0.015. Incidences of cleft palate were 0/22, 1/22, 0/23 and 0/22 for control through high dose. Gee, 8/8/86, Parker, 8/28/86. Additional data received -analysis of dosing solutions, 058 # 052592, and study now ACCEPTABLE. (Parker 3/13/87). Record 073797 in -139 contains historical control data for exencephaly and cleft palate by litter and by fetus. Reconsideration of the study finds the exencephaly not clearly treatment related and there was no adverse effect at the doses tested. (Gee, 6/15/89)

****036 046686**, "Oral Teratology Study in Mice", (Merck Sharp and Dohme, report TT 85-710-1, 1/18/86). Avermectin, 8, 9 isomer of B₁, 99%; 25 females per group given 0 (sesame oil), 0.015, 0.03, 0.1 or 0.5 mg/kg/day by oral gavage, days 6-15; maternal NOEL = 0.1 mg/kg (nominal) (1 death at 0.5 mg/kg), Developmental NOEL = 0.03 mg/kg (nominal)(**adverse effect of cleft palate**); initially reviewed as unacceptable but upgradeable. Gee, 8/8/86, Parker, 8/28/86. Additional data received, 058 052592, analysis of dosing solutions, and study now ACCEPTABLE. (Parker 3/13/87). Initial review indicated a NOEL of 0.015 mg/kg based on exencephaly. Submission of 073797 on -139 contains historical control data for exencephaly

and cleft palate in CF1 mice. Rereview finds that the exencephaly is not dose related and the incidence falls within historical control range. The cleft palate remains as treatment-related adverse effect. (Gee, 6/16/89) [NOEL corrected to 0.03 (Gee, 5/8/92)]

058 052592, Analytical results for mouse teratology studies conducted with delta 8,9 isomer of Avermectin B1 (TT 84-722-0, TT 84-722-1, TT 85-710-0 and TT 85-710-1). This information is sufficient to upgrade the studies to ACCEPTABLE. (Parker and Gee, 3/13/87)

057 052073, Merck Sharp and Dohme discussion of exencephaly and cleft palate in mice treated with delta 8,9 isomer of Avermectin B1. Selected journal articles. No Worksheet. (Parker, 1/12/87).

096 No record number: Merck, Sharp & Dohme Letter 8/19/87. EPA appraisal of teratogenic response. No change in status. No worksheet. (Parker, 11/22/88).

139 073797, Rebuttal and historical control data for exencephaly and cleft palate by litter and by fetus. Document contains a letter from Dr. William J. Scott, Jr., University of Cincinnati, giving his opinion of the results of the mouse studies. He agreed with Merck scientists that the exencephaly did not appear to be treatment related but the cleft palates were due to avermectin exposure. No worksheet. CDFA response in R890616. Gee, 6/16/89.

SUMMARY: CDFA has examined EPA's discussion and the historical control values previously submitted. CDFA still maintained the developmental NOEL of the delta 8,9 isomer is 0.015 mg/kg/day based on exencephaly (Parker, 11/22/88). With the submission of much more complete historical control data covering 1978 to 1985, by individual study, a reevaluation of the exencephaly incidence was made. CDFA now concurs that the results are equivocal at best and no dose response was found. In addition, examination of the historical control data indicates the percentage of litters with exencephaly is within the range. EPA also concluded that the exencephaly was not treatment related - see 096 (Gee, 6/16/89).

TERATOLOGY, MICE
POLAR DEGRADATES OF ABAMECTIN

120 071746, "L-930,406 (Polar Degradates From Thin Film Dish Photolysis) Oral Developmental Toxicity Study in Mice", (Merck Sharp and Dohme, TT #87-717-0, 6/7/88). L-930,406, Lot # L-930,406-00N001, purity not determined, was administered by oral gavage to groups of 25 Crl:CF-1 BR female mice on days 6-15 of gestation at doses of 0 (vehicle control - 0.5% methylcellulose), 0.25, 0.5, and 1.0 mg/kg/day. There were no signs indicating a MTD was achieved during the course of the study. A slight, non-significant increase in cleft palate at the high dose was not considered to be treatment related. There were no other maternal or developmental observations suggestive of a treatment related effect. Maternal and developmental NOEL = 1.0 mg/kg/day (HDT). Supplemental study with no adverse health effects noted (G. Chernoff, 3/7/90).

121 071747, "Oral Developmental Toxicity in Mice, L-930,463 (Citrus Derived Abamectin Polar Degradates)", (Merck Sharp and Dohme, TT #88-713-0, 11/1/88). L-930,463, Lot # L-930,463-000S001, purity not determined, was administered to groups of 25 mated Crl:CF-1 BR female mice by oral gavage on days 6-15 of gestation at 0 (vehicle control of 0.5% methylcellulose), 0.25, 0.5, and 1.0 mg/kg/day (containing concentrated methanol washings from the surface of vehicle tested citrus, L-930,462 carrier vehicle, at doses of 50, 100 and 200 mg/kg, respectively). Two additional control groups treated with 100 and 200 mg/kg L-930,462 carrier vehicle were also tested. At each of the three treatment doses tested, there was a slight non-significant decrease in maternal weight gain. This was not sufficient evidence to establish a MTD. No treatment related developmental findings were observed. Maternal and Developmental NOEL = 1.0 mg/kg/day (HTD). Supplemental study with no adverse health effects noted (G. Chernoff, 3/7/90).

121 071748, "Abamectin Polar Degradates Derived from Citrus Fruits for use in Toxicity (Teratology) Testing", (Merck Sharp and Dohme Research Laboratories, PLM#-3,-4, 11/8/88). Three reports describing the generation and isolation of polar degradates of Abamectin in

citrus, which were used for the teratology study in CDFA Record No. 071747. Supplemental information, no worksheet provided (G. Chernoff, 3/14/90).

GENE MUTATION

009 046621, "Salmonella", (Merck Sharp and Dohme 1976). Avermectin B_{1a}, no purity stated, ± rat liver activation - aroclor or phenobarbital-induced; lot 00P02 at 0, 1, 10, or 100 ug/plate, lot 00P08 at 0, 20, 200, or 2000 ug/plate; strains TA1537, TA92, TA98 and TA100; UNACCEPTABLE and NOT UPGRADEABLE (Gee, 8/5/86).

033 046663, "Salmonella Strains TA1535, TA1537, TA1538, TA98 and TA100", (Merck Sharp & Dohme - 1982). Avermectin, 94% purity, ± rat liver activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate in triplicate, 1 trial; ppt at 3000 and 10,000 ug/plate; no evidence of increased reversion rate. incomplete (no individual plate counts); UNACCEPTABLE (Gee, 8/1/86).

**033 046664, "Chinese Hamster V79 Cells", (Merck Sharp and Dohme - 1983; 8-1-86). Avermectin, 94% purity, ± S-9, rat liver, two trials; 0, 0.03, 0.04, 0.045; 0.05 mM + S-9; 0, 0.003, 0.004, 0.005 and 0.006 mM, -S9; no increase in mutation frequency to cytotoxic concentrations; ACCEPTABLE. (Gee, 8/1/86).

033 046667, "Salmonella, 5 Strains", (Merck Sharp & Dohme - 1986). Avermectin, 89% purity, TA1535, TA1537, TA1538, TA98, TA100 - No activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate; no increased reversion rate; UNACCEPTABLE and NOT UPGRADEABLE. (Gee, 8/4/86).

**033 046668, "Salmonella", (Merck Sharp & Dohme - 1986). Avermectin, 94% purity, TA1535, TA1537, TA1538, TA98, and TA100 ± rat liver activation at 0, 3, 10, 30, 100, or 1000 ug/plate in triplicate; no evidence of increased reversion rate. Considered ACCEPTABLE along with other studies in Salmonella. (Gee, 8/5/86).

GENE MUTATION
DELTA 8,9-ISOMER of AVERMECTIN

120 071742, "L-652,280 (Delta 8, 9-Isomer, Avermectin B₁) Microbial Mutagenesis Assay", (Merck Sharp and Dohme, TT #87-8046, 6/7/88). Delta 8,9 isomer of MK-0936, 91.6%; tested with Salmonella typhimurium strains TA1535, TA97a, TA98 and TA100 and with Escherichia coli strains WP2, WP2 uvrA, WP2 uvrA pKM101; tested with and without Aroclor 1254-induced rat liver activation; at 0 (DMSO), 10, 30, 100, 300, 1000 or 3000 g/plate, triplicate plates; precipitate formed at 3000 g/plate; no individual plate counts, mean only; no evidence of an increase in reversion rate in any strain. Supplemental study on isomer. (Gee, 3/12/90)

GENE MUTATION
POLAR DEGRADATES OF ABAMECTIN

120 071745, "L-930,406 (Polar Degradates From Thin Film Dish Photolysis) Microbial Mutagenesis Assay", (Merck Sharp and Dohme, TT #87-8047 & #87-8058, 6/7/88). L-930,406-000N001, polar degradates from MK-0936; tested with Salmonella typhimurium strains TA1535, TA97a, TA98 and TA100 and with Escherichia coli strains WP2, WP2 uvrA and WP2 uvrA pKM101; with and without Aroclor 1254-induced rat liver activation; concentrations of 0 (DMSO), 100, 300, 1000, 3000 or 10,000 g/plate, triplicate plates, 48 hour incubation; precipitation at the highest concentration but no evidence of cytotoxicity; two trials with activation; positive controls gave expected results without activation but not with activation in trial 1, hence the repeat; no clear increase in reversion rate. No individual plate counts. **Supplemental** study. (Gee, 3/12/90)

CHROMOSOME EFFECTS

033 046666, "Chromosome-in vivo Mouse Chromosomal Aberrations", (SRI-1983). Avermectin, 94% purity, 0, 1.2, 4.0 or 12.0 mg/kg by oral gavage to 12 (control) or 8 (test group) male mice;

sacrificed at 6, 24 or 48 hours; no evidence of increase in aberrations; pilot study included; UNACCEPTABLE but UPGRADEABLE. (Gee, 8/4/86).

**033 046669, "Chromosome-in vitro Aberrations", (Merck Sharp & Dohme-1986). Avermectin, 94% purity, CHO-WBL cells; \pm rat liver activation -beta-Naphthaflavone and phenobarbital induced; 0, 0.01, 0.015, and 0.02 mM scored at 10.5 and 24 hours -S9; 0, 0.005, 0.010, 0.015 or 0.02 at 10.5 hours +S9; 3 hour exposure; no evidence for increased aberrations to cytotoxic levels; ACCEPTABLE. (Gee, 8/5/86).

DNA DAMAGE

**033 046665, "844 MUTA-DNA; Alkaline Elution with Rat Hepatocytes", (Merck Sharp & Dohme, in vitro (TT82 8520, TT82 8523, TT82 8525 and TT82 8526 - 1982 and in vivo (TT83 8302 - 1983)). Avermectin, 4 in vitro trials at 0 to 0.6 mM; 1 in vivo trial in rats; at 10.6, 3.5, or 1.06 mg/kg/male rat by oral gavage; 3 hours exposure in both types; no increase in SS breaks without increased cytotoxicity in vitro; no effects in vivo; ACCEPTABLE. (Gee, 8/1/86).

NEUROTOXICITY

Not required at this time.

OTHER

CLINICAL, IVERMECTIN

144 085368, "The Chemotherapy of Onchocerciasis X. An assessment of four single dose treatment regimes of MK-933 (Ivermectin) in human onchocerciasis", (K. Awadzi, K.Y. Dadzie, H. Shulz-Key, D.R.W. Haddock, H.M. Gilles, and M.A. Aziz; Annals of Tropical Medicine and

Parasitology, 79 (1):63-78, 1985). A publication with supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

144 085369, "The Effects of Ivermectin on Transmission of Onchocerca volvulus", (E.W. Cupp, M.J. Bernardo, A.E. Kiszewski, R.C. Collins, H.R. Taylor, M.A. Aziz, and B.M. Greene; Science, 231:740-742, 1986). A publication with supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

144 085370, "Comparison of Ivermectin and Diethylcarbamazine in the Treatment of Onchocerciasis", (B.M. Greene, H.R. Taylor, E.W. Cupp, R.P. Murphy, A.T. White, M.A. Aziz, H. Shulz-Key, S.A. D'Anna, H.S. Newland, L.P. Goldschmidt, C. Auer, A.P. Hanson, S.V. Freeman, E.W. Reber, and P.N. Williams; New England Journal of Medicine, 313 (3):133-138, 1985). A publication with supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

144 085372, "Mectizan (Ivermectin, MSD)", (Merck Sharp and Dohme Product Monograph). Supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).